Table 1

Patients with follow-up data	Macitentan (N=1512)	Macitentan and riociguat (N=125)
Patients with ≥1 AE, n (%)	1075 (71.1)	90 (72.0)
Most common (≥7%) AEs*, n (%)		
Dyspnoea	272 (18.0)	17 (13.6)
Peripheral oedema	133 (8.8)	11 (8.8)
Headache	119 (7.9)	7 (5.6)
Pneumonia	97 (6.4)	9 (7.2)
Oedema	95 (6.3)	14 (11.2)
AEs of special interest, n (%)		
Syncope	39 (2.6)	2 (1.6)
Haemoptysis	14 (0.9)	2 (1.6)

*Patients could have had multiple AEs.

Conclusion: OPUS is the largest cohort of patients newly treated with macitentan and provides insight into real-world treatment, including combination therapy with macitentan and riociguat. These data show that there are no unexpected safety findings with this combination in patients with PH.
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P3561
Active selexipag-metabolite MRE-269 induces DUSP1 and inhibits PASMC proliferation

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Background: It has been reported that the increased activity of p38 MAP kinase (p38MAPK) in pulmonary artery smooth muscle cells (PASMCs) plays a pathogenic role in pulmonary arterial hypertension (PAH). Dual specificity protein phosphatase 1 (DUSP1), an archetypical member of MAPK phosphatases, dephosphorylates and deactivates activated p38MAPK. Protein kinase A (PKA) is known to induce DUSP1 by phosphorylating cAMP response element binding protein. Prostacyclin (PGI2) has been used as effective therapy for PAH, while the detailed mechanism is not clarified. It binds to IP receptor resulting in the conversion of ATP to cyclic AMP (cAMP) which increases PKA activity. Selexipag, a non-prostanoid IP receptor agonist, was recently authorized for use to treat PAH. Selexipag is metabolized into active metabolite, MRE-269, which has a high affinity for the IP-receptor.
Purpose: To assess whether IP receptor agonist MRE-269, an active metabolite of selexipag, induces DUSP1 and inhibits PASMC proliferation.
Methods: We stimulated PASMCs or endothelial cells (PAECs) by BMP2 (10 ng/mL), ET-1 (100 nM), PGI2 (10 ng/mL), MRE-269 (300 nM), or the combination of them in vitro. PH-797804 (10–100 nM) was used as a selective inhibitor of p38MAPK. Quantitative PCR was performed to quantify mRNA expressions of DUSP1, cyclin D1, and GAPDH. Cell proliferation was assessed by CCK8 cell proliferation assay kit. We used combination of ET-1 and BMP2 to activate p38MAPK as we have reported previously.
Results: In PASMCs, PGI2 increased DUSP1 expression slightly but significantly. MRE-269 increased DUSP1 and decreased cyclin D1 in PASMCs. Combination of BMP2 with ET-1 pretreatment significantly accelerated the proliferation of PASMCs, while PH-797804 totally abrogated it, suggesting this proliferation was induced by p38MAPK. The accelerated proliferation by ET-1 and BMP2 was attenuated also by MRE-269. In contrast, MRE-269 did not affect the expressions of DUSP1 or cyclin D1 in PAECs.
Conclusions: The p38MAPK accelerates proliferation of PASMC in certain pathological conditions, such as exposure to ET-1. MRE-269 induces DUSP1 in PASMCs, and inhibits the p38MAPK-mediated proliferation of PASMCs.

P3562
The relationship between pulmonary artery pressures and bleeding volume in balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

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Background: The balloon pulmonary angioplasty (BPA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) is still an emerging procedure. Pulmonary bleedings by BPA is a complication to be overcome.
Purpose: The aim of this study is to evaluate the relationship between hemodynamic parameters and the severity of bleedings.
Methods: Computerised tomography (CT) were performed immediately after 131 consecutive BPA sessions and quantified the bleeding volumes. Assuming that the bleedings were ellipsoid, the pulmonary bleeding volumes were estimated (Figure). The correlation between hemodynamic parameters and the bleeding volumes were evaluated.
Results: Pulmonary bleedings were identified in 61 of 131 sessions (46.6%). The median of bleeding volume was 4.9ml. Hemodynamic parameters were not associated with the frequency of pulmonary bleeding. However, the bleeding volume was significantly correlated with mean pulmonary artery pressure (mPAP) before BPA (Spearmans's ρ=0.30, p=0.023).

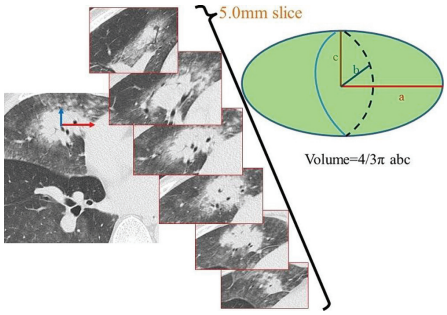

Figure 1. Quantification of bleeding volume

Conclusions: Hemodynamic parameters are not related to bleeding frequency, but once bleeding, the high mPAP is associated with increase of bleeding volume. mPAP is useful for risk stratification of BPA.

P3563
Risk factors for bleeding in patients with venous thromboembolism during long-term anticoagulation therapy: From the COMMAND VTE Registry

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Background: Venous thromboembolism (VTE) has a long-term risk of recurrence, and the current guidelines recommend prolonged anticoagulation therapy for high-risk patients of recurrence if they are low risk of bleeding. However, risk factors associated with bleeding events during long-term anticoagulation therapy have not been well characterized in patients with VTE.
Purpose: We sought to investigate risk factors for major bleeding in patients with VTE during anticoagulation therapy.
Methods: The COMMAND VTE Registry is a multicenter registry enrolling 3027 consecutive patients with acute symptomatic VTE objectively confirmed by imaging examination or by autopsy among 29 centers in Japan between January 2010 and August 2014. After excluding patients with mortality (n=73), major bleeding events (n=41), loss to follow-up (n=32) within 10 days after diagnosis, and those without anticoagulation therapy beyond 10 days after diagnosis (n=153), the current study population consisted of 2728 patients who received anticoagulation therapy beyond the acute phase. Consistent with previous reports, we selected the 10 clinically relevant risk-adjusting variables (age, sex, location of thrombus, transient risk factor, active cancer, prior major bleeding, chronic kidney disease, liver failure, anemia, and thrombocytopenia), and we used a multivariable Cox proportional hazard model to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of variables for the International Society of Thrombosis and Hemostasis (ISTH) major bleeding events during anticoagulation therapy.
Results: The mean age was 67±15, and 1671 (61%) were female. During the median follow-up period of 555 (interquartile range, 168–1241) days, major bleeding events occurred in 189 patients (6.9%). Patients with major bleeding had significantly smaller body weight (56.3±12.4 kg vs. 58.4±13.8 kg, P=0.043), higher prevalence of active cancer (38% vs. 20%, P<0.001), prior major bleeding (13% vs. 6.0%, P<0.001), anemia (hemoglobin level <13 g/dl for men, <12 g/dl for women, 67% vs. 52%, P<0.001), thrombocytopenia (platelet count <10000 /μL, 10% vs. 4.7%, P=0.003), and significantly lower prevalence of transient risk factors for VTE (28% vs. 35%, P=0.032). Age, gender, location of thrombus, prevalence of chronic kidney disease, liver failure were comparable between patients with and without major bleeding. Cox regression analysis showed that active cancer (HR 2.88, 95% CI 2.10–3.92), prior major bleeding (HR 2.37, 95% CI 1.50–3.58), anemia (HR 1.82, 95% CI 1.32–2.53) and thrombocytopenia (HR 2.06, 95% CI 1.23–3.24) were independently associated with an increased risk for major bleeding.
Conclusions: In real-world VTE patients, active cancer, prior major bleeding, anemia and thrombocytopenia were the independent risk factors for major bleeding during long-term anticoagulation therapy.
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